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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,930	05/23/2006	Peter William Surman	D2026/20001	3207

3000 7590 10/29/2010

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EXAMINER	
VU, JAKE MINH	
ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
10/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@crbcp.com

Office Action Summary	Application No.	Applicant(s)	
	10/561,930	SURMAN ET AL.	
	Examiner	Art Unit	
	JAKE M. VU	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 30-50* is/are pending in the application.

4a) Of the above claim(s) *39-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,30-38,46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Applicant's Amendment, Declaration, and Information Disclosure Statement filed on 08/10/2010.

- Claims 27 and 30 have been amended.
- Claims 28-29 have been cancelled.
- Claims 46-50 have been added.
- Claims 39-45 have been previously withdrawn from consideration.

Declaration under 37 CFR 1.132

The Declaration under 37 CFR 1.132 filed 08/10/2010 is insufficient to overcome the rejection of claims 27, 30-38, 46-50 as set forth in the last Office action because of the reasons discussed below in the Response to Argument section.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27, 30-33, 35, 36, 47-48 rejected under 35 U.S.C. 102(b) as being anticipated by EISHUN (JP 10-175865) **are maintained** for reasons of record in the previous office action filed on 03/01/2010 and as discussed below in the *Response to Argument* section.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27, 30-38, 47-49 rejected under 35 U.S.C. 103(a) as being unpatentable over EISHUN (JP 10-175865) in view of HONMA et al (US 6,569,903), ALI et al (US 5,521,222) and HORLINGTON (US 4,425,346) **are maintained** for reasons of record in the previous office action filed on 03/01/2010 and as discussed below in the *Response to Argument* section.

Upon further consideration, a new ground(s) of rejection is made as discussed below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 27, 30-34, 36-38, 46-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over RAMUTH et al (*A liquid clozapine preparation for oral administration*

in hospital. Pharm J 1996; 257: 190-1) as evidence by WALKER et al (Stability of Clozapine Stored in Oral Suspension Vehicles at Room Temperature. Canadian J Hospital Pharmacy. 58:5. (2005) in view of REMINGTON (Remington: The Science and Practice of Pharmacy 20th edition (2000). pg. 245 and 273-274) and EISHUN (JP 10-175865).

Applicant's claims are directed to a composition comprising of: 0.1-10% of clozapine; a buffer system of sodium phosphate/sodium hydroxide for a pH of 6-8; a wetting agent; such as propylene glycol or glycerin; a preservative, such as methylparaben; and a sweetener.

RAMUTH teaches a clozapine suspension composition comprised of: 1000mg of clozapine in 50mL of Guy's hospital formula base solution (see pg. 190, under Preparation of clozapine suspension), which would be a 2% concentration. The Guy's hospital formula base contains: syrup, which would read on sweetener; methylhydroxybenzoate, which is methylparaben; and carboxymethylcellulose, which is a thickening/suspending agent. No tests for microbiological stability have been performed on the suspension, but the suspension is considered stable for at least 18 days (see pg. 292 under Discussion).

RAMUTH does not teach using a buffer system of sodium phosphate/sodium hydroxide for a pH of 6-8; or a wetting agent; such as propylene glycol or glycerin.

WALKER disclosed that oral suspensions of clozapine in Ora-Sweet, Ora-Plus, simple syrup, or Guy's pediatric mixture (the vehicle discussed in RAMUTH) are able to

retain more that 95% of the initial concentration for 63 days. The stability end point was not determined.

REMINGTON teaches optimization of pH and buffer for drug stabilization. (see pg. 245, 273-274).

EISHUN (JP 10-175865) teaches common pH buffer systems include sodium phosphate.

The references do not specifically optimizing pH as claimed by Applicant. The pH of a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize using a buffer system, such as sodium phosphate. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results, such as drug stabilization as discussed in REMINGTON. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of pH would have been obvious at the time of Applicant's invention.

Response to Arguments

Applicant argues that the Eishun (JP 10175865) reference describes a solution (i.e., not a suspension) intended for application to the eye (i.e., not oral administration) of up to 0.5% clozapine. The Eishun reference teaches formulations for eye drops.

The Examiner finds this arugment unpersuasive, because Applicant's claims recite a composition, and the intended use recited in the preamble would reasonably appear not to be a claim limitation. "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim...If, however, the body of the claim fully and intrinsically sets forth the complete invention, including all of its limitations, and the preamble offers no distinct definition of any of the claimed invention's limitations, but rather merely states, for example, the purpose or intended use of the invention, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." Pitney Bowes, Inc. v. Hewlett Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). Thus, the intended use of oral administration in the composition claims is met by the prior art, because the prior art compositions would be at least capable of performing said use.

Applicant argues that Eishun's compositions are not true suspensions in which clozapine particles are suspended in a matrix. In addition, it is known in the art that clozapine is unsuitable for formulating as a solution due to its very low solubility. While a solution of clozapine may be appropriate for use in the eye, due to the sensitivity of the tissues in the eye and the necessity of using low doses of clozapine, the low solubility in water makes a solution of clozapine impracticable for oral administration due to the larger dose necessary for oral administration.

The Examiner finds this argument unpersuasive, because as Applicant stated that clozapine has low solubility. In fact, clozapine is practically insoluble in water. Thus, the EISHUN's composition could not be a true solution, but rather a suspension. EISHUN's term for solution seems to interpret as a liquid formulation, since EISHUN also discussed formulating ointment, which is not a liquid but thick as a gel. Additionally, EISHUN disclosed using stabilizers and emulsifying agents, such as carboxymethylcellulose, which are not commonly used in true solutions, but rather suspensions. EISHUN's composition has a concentration of 0.5%, which is in the same range as claimed by Applicant in the dependent claims. Note, Applicant's independent claims do not recite a concentration.

Applicant argues that it is known in the art that suspensions may cause irritation when applied to the eye, as disclosed in U.S. Patent No. 4,558,066 (Waterbury), which teaches (col. 22, lines 58-61): Suspensions have the advantage of more extended action and the disadvantage that it is difficult to avoid the presence of a few particles which are large enough to cause irritation.

The Examiner finds this argument unpersuasive, because EISHUN disclosed filtering the composition, which would avoid the few particles which are large enough to cause irritation.

Applicant argues that the Declaration filed on 08/10/2010 shows unexpected result with a stability of 2 years.

The Examiner finds this argument unpersuasive, because in order to overcome a prima facie case of obviousness, it is incumbent upon the Applicant to provide

comparative test evidence that demonstrates unexpected superiority of the claimed compositions versus the closest prior art compositions, and not simply an advantage predictable from the prior art. See *In re Chapman*, 148 USPQ 711, 715 (CCPA, 1966). Moreover, such proffered comparisons must be commensurate in scope with the breadth of the claims. See *In re Clemens*, 206 USPQ 289, 296 (CCPA, 1980) and *In re Coleman*, 205 USPQ 1172, 1175 (CCPA 1980). In this instance, Applicant's claims are not commensurate in scope with the breadth of the claims. Applicant's claim 27 recite the pH of 6-11, but the pH of the comparison formulation has a pH of 7.2 (see pg. 2 of Declaration).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephonic Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAKE M. VU whose telephone number is (571)272-8148. The examiner can normally be reached on Mon-Tue and Thu-Fri 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618